REMARKS

Reconsideration of the present application in view of the present amendments and the following remarks is respectfully requested. Claims 2, 4, 5, 7-14, 99, and 100 are currently pending in this application. Applicants acknowledge and thank the Examiner for indicating that the subject matter of claims 2, 4, and 5 is allowable. Applicants have amended claims 7, 11, 12, and 99 to more clearly define certain subject matter of Applicants' invention and to place the claims in condition for allowance. Support for the amended claims may be found in the specification, for example, at page 12, lines 1-14; page 16, lines 4-13; and the Sequence Listing. No new subject matter has been added.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

The PTO rejects claims 8-14 and 99-100 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The PTO asserts that the specification does not provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention in a manner that is reasonably correlated with the scope of the claims. More specifically, the PTO alleges that the specification does not provide sufficient guidance with respect to how to make a variant polynucleotide that will be 90% identical to SEQ ID NO:1 or that will be 90% identical to a polynucleotide that encodes a polypeptide comprising an amino acid sequence of SEQ ID NO:2 and that has the desired substrate specificity or the desired dephosphorylating activity.

Applicants respectfully traverse this rejection and submit that as disclosed in the present specification and recited in the instant claims, Applicants fully enabled the claimed invention at the time the instant Application was filed. Applicants submit that the specification provides explicit guidance enabling a person skilled in the art to make and use the claimed polynucleotides, readily and without undue experimentation. As taught in the present specification, the claimed polynucleotides encode a dual specificity phosphatase-12 (DSP-12) polypeptide that has the ability to dephosphorylate phosphorylated tyrosine and serine/threonine residues of a DSP-12 substrate (*e.g.*, at page 9, line 26 through page 10, line 3).

Applicants submit, contrary to the PTO's assertions, that the instant claims are commensurate in scope with the disclosure of the specification and that the specification enables

a skilled artisan to make and use the claimed polynucleotides, including polynucleotide variants. In certain embodiments, the Application teaches how to make and use a polynucleotide variant that comprises a nucleotide sequence that is at least 90% identical to the sequence of a polynucleotide encoding a polypeptide comprising SEQ ID NO:2. As provided by the specification, in particular according to its teachings of how to make and use SEQ ID NOS:1 and 2 in view of art-accepted methodologies, such a polynucleotide variant encodes a polypeptide having (i) an aspartic acid located at a position corresponding to position 222 of SEQ ID NO:2 and (ii) the peptide sequence CLVHCKMGVSRSASTVIAYAM (SEQ ID NO:3) located at positions corresponding to positions 249 through 269 of SEQ ID NO:2. As also clearly provided by the specification, whether an unknown polynucleotide shares 90% identity with a polynucleotide encoding a DSP-12 polypeptide can be readily determined by aligning either the polynucleotide sequence or the polypeptide sequence that it encodes, according to alignment methods described therein and known in the art (*see, e.g.*, page 14, lines 7-15). As also taught in the specification and recited in the claims, this polynucleotide variant encodes the DSP-12 polypeptide having the sequence of SEQ ID NO:2, but the polynucleotide differs from a disclosed nucleotide sequence that encodes SEQ ID NO:2 (*e.g.*, SEQ ID NO:1) due to degeneracy of the genetic code (*see, e.g.*, page 14, lines 21-26). The degeneracy of the genetic code is a basic principle of the molecular biology art that is well known and routinely used by persons skilled in the art. A person skilled in the art is therefore unquestionably enabled by the instant specification to make the claimed polynucleotides, including these variants and also to use such polynucleotide variants without undue experimentation, for example, in screening and detection assays.

Applicants further submit that in view of the abundant guidance and direction provided in the specification, the advanced state of the art, and the high level of skill of a person practicing the art, the specification enables a skilled artisan to make and use a polynucleotide variant that encodes a DSP-12 polypeptide, readily and without undue experimentation. (*See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). As discussed in detail herein, the specification teaches a skilled artisan how to make and use a claimed polynucleotide variant that exhibits at least 90% sequence identity to a polynucleotide encoding a polypeptide that comprises the amino

acid sequence of SEQ ID NO:2 (*e.g.,* the polynucleotide of SEQ ID NO:1), that encodes a DSP-12 polypeptide capable of dephosphorylating a DSP-12 substrate, and that comprises a sequence that encodes the active site peptide sequence SEQ ID NO:3 (*see generally* page 12, lines 1-19; page 13, line 27 through page 14, line 20; page 16, lines 4-13).

A description of which amino acid residues or which polypeptide region, if changed, could affect phosphatase activity, that is, what changes in the structure of a DSP-12 polypeptide variant affect the function of the variant, is most useful to the skilled artisan wishing to practice the claimed invention. By understanding which amino acids contribute to dephosphorylation activity and thus are less amenable to modification, a skilled artisan may reasonably and rationally predict that modifications not affecting catalytic activity may be made to residues that are not implicated in catalytic activity. According to textbook knowledge in the molecular biology arts, "[in] fact, evidence now indicates that amino acid replacements in many parts of a polypeptide chain can occur without seriously modifying catalytic activity" *(see Molecular Biology of the Gene*, page 227 (James D. Watson et al., ed., The Benjamin/Cummings Publishing Co., (Menlo Park, CA) (4th ed. 1987). Particularly, as taught in the specification and understood in the art, a skilled artisan would expect that the secondary structure and hydropathic nature of the DSP-12 polypeptide would be substantially unchanged if a conservative amino acid substitution were made to such residues, that is, conservative modifications would be tolerated (*see, e.g.,* specification at page 11, lines 16-30). Given the disclosure in the specification of a polynucleotide (*e.g.,* SEQ ID NO:1) encoding a DSP-12 polypeptide (SEQ ID NO:2) and methods taught in the specification and known in the art for making and identifying DSP-12 variants with phosphatase activity (*e.g.,* page 13, line 27 through page 14, line 26; page 16; line 26 through page 17, line 6; page 32, lines 2-14), a skilled artisan need not, and is not required to, determine "all the DSP-12 polypeptides having the desired biological characteristics," as asserted by the PTO (Action, page 4) but instead is enabled by the instant disclosure to make and use the claimed polynucleotide variants readily and without undue experimentation.

Applicants respectfully submit that, contrary to the assertion by the PTO, the specification teaches a person skilled in the art the structural and functional properties of a DSP-12 polypeptide variant encoded by the claimed polynucleotide variants. As taught in the present

specification (*e.g.*, at page 9, line 26 through page 10, line 6) and recited in the instant claims, polynucleotides that encode a DSP-12 polypeptide, or a variant thereof, have the ability to dephosphorylate phosphorylated tyrosine and serine/threonine residues of a DSP-12 substrate (*i.e.*, a *functional property*). Methods for detecting DSP-12 catalytic activity are taught in the specification (*see, e.g.*, page 32, lines 2-14). The specification further describes as a *structural* feature the conserved dual specificity phosphatase signature active site motif, C-X_5-R, which is present in the peptide CLVHCKMGVSRSASTVIAYAM (SEQ ID NO:3) (motif underlined) within the DSP-12 polypeptide sequence encoded by the claimed polynucleotides (*see, e.g.*, page 16, lines 4-13; page 38, lines 7-12, and references cited therein; SEQ ID NO:1 and SEQ ID NO:2; *see also, e.g.*, Keyse, *Biochim. Biophys. Acta* 1265:152-60 (1995)). Also, as understood in the art and described in the specification, substitution of the cysteine residue within this active site motif results in a loss of phosphatase activity (*see, e.g.*, page 10, line 17 through page 11, line 15, and references cited therein). The specification also describes that when an invariant aspartic acid residue at position 222 in SEQ ID NO:2 is substituted with another amino acid, the resulting polypeptide, called a substrate trapping mutant, has a reduced ability to dephosphorylate a substrate (*see id.*). Thus, the specification has identified a region (SEQ ID NO:3) and positions within the DSP-12 polypeptide (an invariant aspartate residue and a cysteine residue within the active site motif) that are not amenable to modification, and if mutations are introduced at these positions, the resulting polypeptide has reduced catalytic activity.

Applicants also respectfully disagree with the assertion by the PTO that screening for multiple modifications is not routine. Random mutagenesis techniques, such as alanine scanning mutagenesis, error prone polymerase chain reaction mutagenesis, and oligonucleotide-directed mutagenesis, some of which generate tens of thousands of mutants, are well known and have been used extensively in the art (*see, e.g.*, Sambrook et al. *Molecular Cloning: A Laboratory Manual*, 3rd ed., Cold Spring Harbor Laboratory Press, NY (2001)). Even assuming *arguendo*, as the PTO asserts, that it cannot be predicted which positions within a protein's sequence can tolerate a substitution, deletion, or insertion of an amino acid, persons skilled in the art can alleviate these difficulties by developing independent assays for assessing folding of the protein of interest (*see, e.g.*, Sambrook et al., page 13.3). Such assays commonly include, for

example, the ability of the protein to react with mono- or polyclonal antibodies that are specific for native or unfolded epitopes, the retention of catalytic or ligand-binding functions, the sensitivity or resistance of the mutant protein to digestion with proteases, and other functional assays that characterize a particular polypeptide (*see* Sambrook et al., page 13.3; *see also, e.g.,* specification at page 22, line 27 through page 24, line 27; page 25, line 1 through page 27, line 9; page 32, lines 1-14). Sambrook et al. further teach that the functions of proteins can be mapped to specific structural domains, undesirable activities of enzymes can be eliminated, and their desirable catalytic and physical properties can be enhanced. "In short, oligonucleotide-mutagenesis has become the genetic engineer's alchemy." (Sambrook et al., page 13.4).

While identifying DSP-12 variants generated by any of the commonly used mutagenesis techniques may involve screening a large number of molecules, such experimentation is not undue. To determine the phosphatase activity of a DSP-12 variant, a skilled artisan, using methods provided in the specification and known in the art, can readily analyze dephosphorylation of a DSP-12 substrate (*see, e.g.,* page 21, line 19 through page 22, line 24; page 32, lines 1-14). Given the teachings of the present specification and, *inter alia*, the level of skill in the art, performing such assays to determine whether an encoded polypeptide has DSP-12 phosphatase activity would not amount to undue experimentation, but instead is merely a matter of permissible routine screening. (*See In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (The test for enablement is not merely quantitative "since a considerable amount of experimentation is permissible.")).

Applicants also respectfully disagree with the assertion by the PTO (*see* Action, page 4, lines 5-7) that a skilled artisan in the protein engineering art would expect tolerance of a protein to structural modification without compromising the protein's activity to diminish with each further and additional modification (*e.g.,* multiple amino acid substitutions). In *Molecular Biology of the Gene*, *supra*, Watson et al. note that "the conclusion that minor changes to amino acid sequence do not significantly alter enzyme activity is extended to the finding that some mutations that convert inactive mutant enzymes to active forms may work by causing a second amino acid replacement in the mutant enzyme." (*See Molecular Biology of the Gene, supra*, page 228.) Furthermore, skilled artisans may introduce mutations into a protein to enhance, not

diminish, its function, for example to improve the binding affinity and specificity of an antibody, and believe that "it is foreseeable that there will be examples where optimization of an antibody will require multiple mutations distributed among several CDRs." (Huse et al., *Intern. Rev. Immunol.* 10:129-37 (1993), which is enclosed for the Examiner's convenience). Such optimization via multiple mutations has in fact been achieved (*see, e.g.,* Yelton et al., *J. Immunol.* 155:1994-2004 (1995), enclosed for the Examiner's convenience). Therefore, a person skilled in the dual specificity phosphatase art would reasonably believe that multiple modifications of a DSP-12 polypeptide would not necessarily adversely affect its substrate binding properties and/or catalytic properties.

As discussed in detail herein, the instant claims encompass a finite number of highly related polynucleotides, and the specification provides ample guidance for a skilled artisan to make and use the claimed polynucleotides and their encoded products readily and without undue experimentation. Furthermore, it is well settled that an Applicant need not test every embodiment of an invention encompassed by a claim and need not describe a large number of examples to enable a person skilled in the art to make and use the invention, particularly in a case such as this one where the level of skill of an artisan practicing the art is high and the teachings of the specification are ample. *See In re Strahilevitz*, 212 U.S.P.Q. 561, 563 (C.C.P.A. 1982) (finding that although the invention encompassed a large variety of compounds, a large number of examples would not be required because examples are not required to satisfy section 112, first paragraph). Moreover, even though a large number of polynucleotide variants may be made, Applicants are not required to list all operable embodiments of the invention and to exclude inoperable ones, if any. *See Atlas Powder Co. v. E. I. Dupont de Nemours & Co.* 750 F.2d 1569, 1576 (Fed. Cir. 1984).

Accordingly, Applicants submit that given the disclosure of the present Application, the state of the art, and the level of a skilled artisan practicing the art, the specification enables a skilled artisan to make and use the claimed polynucleotides, readily and without undue experimentation. Applicants therefore respectfully submit that the Application satisfies all requirements under 35 U.S.C. § 112, first paragraph, and request that the rejection of the claims be withdrawn.

REJECTION UNDER 35 U.S.C. § 101

The PTO rejects claims 7-10, and 12-14 under 35 U.S.C. § 101, asserting the claims are directed toward non-statutory subject matter. The PTO alleges that naturally occurring proteins and/or nucleic acids are non-statutory subject matter.

Applicants respectfully submit that the basis for this rejection is obviated in view of the Amendments submitted herewith. Amended claim 7 is directed to an *isolated* polynucleotide comprising the sequence set forth in SEQ ID NO:1. Applicants submit that claim 7 and claims 8-10 and 12-14, which depend on claim 7, are directed to statutory subject matter as required under 35 U.S.C. § 101, and request that the rejection of the claims be withdrawn.

Applicants respectfully submit that all claims in the Application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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Enclosures:

Huse et al., *Intern. Rev. Immunol.* 10:129-37 (1993)
Yelton et al., *J. Immunol.* 155:1994-2004 (1995)
Notice of Appeal

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